REMARKS

I. Status of the Application

Claims 34-64 were pending in the application at the time the Office Action was mailed. Claims 39, 41-43 and 51-64 have been withdrawn from consideration. Claims 34-38, 40 and 44-50 were rejected and no claims were allowed. By this Response, claims 34 and 44-50 are amended, claim 40 is canceled, and no claims are added. Therefore, claims 34-38 and 44-50 are now before the Examiner for consideration.

Applicant appreciates the Examiner's offer to record official notice of the interview granted on March 8, 2007; Applicant takes the substance of the interview into consideration in preparing this response.

II. Election

Applicant acknowledges the Examiner's holding of the restriction requirement as final.

III. Specification

The specification has been objected to for lacking a sequence listing accompanied by a computer readable form. Please find concurrently electronically submitted a sequence listing in a .txt file format. The sequence listing includes no new matter. The specification is herein amended to include the sequence listing by reference.

IV. Claim Objections

Claims 49 and 50 are objected to for listing an intended use rather than setting forth an additional step to the method. As currently amended, claims 49 and 50 now further limit the scope of the claimed method rather than set forth an intended use. Applicant believes the forgoing amendments fully address this objection.

V. Claim Rejections

A. Claim Rejection under 35 U.S.C. § 112

Claims 34-38, 40 and 44-50 are rejected under 35 U.S.C. § 112 as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Particularly, the Examiner rejects the use of the phrase "human transketolase like-1" in the aforementioned claims, and requests the gene rather be identified with a SEQ ID number. Applicant has revised claim 1 to replace "human transketolase like-1" with "polynucleotides whose complement hybridizes under stringent conditions to a sequence having at least 80% homology to SEQ ID.: 1." This amendment is supported by page 7 lines 23-26, page 7 lines 30 – page 8 line 3, and page 9 lines 26-30. In light of the foregoing amendment to claim 34, Applicant cancels claim 40, as it no longer limits the scope of what is being claimed.

Additionally, Claims 34-38, 40 and 44-50 are rejected as being incomplete for omitting essential steps. Particularly, the Examiner indicates that the use of the term "overexpression" in the claims requires that a comparative "normal expression" be defined. Applicant has revised the relevant language to define a comparative level of expression in a "control test sample". Support for the amendment to claim 34 may be found on page 24 lines 1-3 of the application as filed.

Furthermore, claim 48 is rejected due to improper antecedent basis. Applicant has amended claim 48 to include the requisite antecedent basis.

Applicant respectfully asserts that the foregoing amendments and remarks fully address the Examiner's rejections under 35 U.S.C. §112, and therefore requests their withdrawal.

B. Claim Rejection under 35 U.S.C. § 102

Claims 34-38, 40, and 44-50 are rejected under 35 U.S.C. § 102(e) as being anticipated by Mack et al. (US 2003/0234820 A1; filed February 27, 2002). Applicant respectfully asserts that Mack et al. fails to teach all the elements of the present claims. For instance, currently amended claim 34 recites in step (c), ". . . abnormal cell proliferation is indicated when the level of expression in the biological test sample is greater than said level of expression in the control test sample." Mack et al does not teach or suggest the element of a comparison of transketolase

like-1 expression in normal versus abnormal cell proliferations. Unlike the present application, Mack et al does not teach transketolase-like 1 ("TKT-L1") to be overexpressed in cancer tissues compared to normal healthy colon tissue. The present application teaches and claims the aforementioned point in claim 34.

The only specific reference Mack et al. makes to transketolase like-1 is found in Table 17, where Mack et al. teaches that the ratio of levels of transketolase like-1 gene in primary tumor samples ("PrimC"), versus liver metastasis samples from patients with metastatic colorectal cancer ("MetC"), is 2.17. This means Mack et al. has found that transketolase like-1 is underexpressed in MetC as compared to PrimC. The current claims recite a method including comparing normal tissue ("NormC") to potentially cancerous tissue, not comparing MetC to PrimC.

Although the Examiner points the Applicant to paragraphs 42-43 in addition to Table 17, Applicant notes that while paragraph 42 broadly references Tables 1-26, the descriptions set forth in paragraph 42 do not specifically relate to Table 17, which contains the only instance of transketolase like-1 in the reference. Applicant believes paragraph 42 specifically relates to Tables 15, 21, and 22 none of which refer to transketolase like-1. Applicant further takes attention of Mack et al pages 21 and 22, specifically paragraph 194. During the March 8, 2007, interview, the Examiner pointed out that paragraph 194 discusses a comparison of expression of certain genes in normal cells to cancerous cells. However, nowhere in Mack et al. is a comparison of the gene of transketolase like-1 in normal versus cancer cells taught.

Not only does Mack et al. not teach TKT-L1 in a comparison of abnormal to normal cells, but Mack et al also fails to teach a comparison of precursor primary cancer tumor cells ("PrimC") to normal healthy cells ("NormC"). In Tables 1-26, Mack et al. investigated hundreds of genes with regard to their expression in primary cancer cells ("PrimC") and cancer metastasis cells ("MetC"), each of colon cancer only. The determined expression values were compared PrimC vs. MetC and MetC v. NormC. There is no information given, if the level of expression in PrimC is higher relative to NormC, as is included in claim 34. Based on the Mack et al patent application TKT-L1 expression in PrimC can be higher, equal to, or lower, compared to NormC.

Mack et al. omits a NormC to Prim C comparison, even though it is well-known in the art that PrimC are the pre-stage to MetC, and would be indicative of abnormal cell proliferation, as claimed by the present application.

Applicants respectfully urge the Examiner to take note that "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The reference in Mack et al to transketolase-like 1 is not associated with the claimed comparison. Further, the claimed comparison of normal to cancerous cells, as disclosed in Mack et al. is at best a disclosure of the genus of expressed genes, and not a teaching of the use of the species of transketolase-like 1. A genus does not always anticipate a claim to a species within the genus. However, when the species is clearly named, the species claim is anticipated. *Ex parte A,* 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990). In Mack et al., the species is not clearly named for the use the Examiner alleges is taught.

Mack et al. fails to teach the specific comparison of sequences homologous to SEQ ID NO: 1 (TKT-L1) in normal cells as compared to in potentially abnormal test cells. Mack et al completely omits any teaching of expression of any genes in PrimC as compared to NormC. Mack et al. only expressly teaches that TKT-L1 expression in MetC is lower than in PrimC. Further, Mack et al. fails to teach that a greater level of expression of sequences having homology to SEQ ID NO: 1 is indicative of abnormal cell proliferation.

Because Mack et al. fails to teach all the elements of the current claims, Applicant respectfully requests withdrawal of this rejection. Should the Examiner remain unconvinced the anticipation argument is not overcome, Applicant respectfully requests the Examiner additionally consider the arguments presented below, which seemed more appropriately categorized as a response to an obviousness rejection.

C. Preemptive Response to Potential 35 U.S.C. § 103 Rejection

To the extent that the pending 102(e) rejection based on Mack et al. may be modified into a 103 rejection, although such a 103 rejection is not presently pending, Applicants respectfully assert that (1) Mack et al. presents no motivation to select the species of transketolase like-1 from the genus of expressed genes in human for a normal to cancerous cell comparison and (2) Mack et al teaches away from the combination.

The Examiner has not established there would be any motivation to use transketolase like-1 in a comparison between normal and cancerous cells. Although Mack et al. teaches transketolase like-1 for use in a PrimC to MetC comparison, and also teaches a comparison of MetC to NormC, transketolase like-1 is not a gene disclosed as useful for the MetC to NormC comparison. Although the Examiner points out that paragraph [0194] refers broadly to a MetC to NormC comparison of the broad genus of "genes", this genus is too broad to suggest the gene of transketolase like-1 without identifiable motivation to combine. See, e.g., *Deuel*, 51 F.3d at 1558-59, 34 USPQ2d at 1215 ("No particular one of these DNAs can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared."); *Baird*, 16 F.3d at 382-83, 29 USPQ2d at 1552; *Bell*, 991 F.2d at 784, 26 USPQ2d at 1531 ("Absent anything in the cited prior art suggesting which of the 10^{36} possible sequences suggested by Rinderknecht corresponds to the IGF gene, the PTO has not met its burden of establishing that the prior art would have suggested the claimed sequences."). In the Mack et al, hundreds or thousands of genes are listed, and the Examiner has not pointed out why one of skill in the art would choose to select TKT-L1 out of those hundreds or thousands of genes, for a use other than that which Mack et al. expressly teaches in Table 17.

Indeed, the TKT-L1 gene is mentioned only one time within the Mack paper, in Table 17, in course of a comparison between MetC and PrimC. Against the background of hundreds of investigated and reported genes, this reference to TKT-L1 is a relatively passing mention with no indication of uses for TKT-L1 other than those reported in Table 17. A person skilled in the art searching for an indicator molecule suitable for the detection of cancerous cells in comparison to normal cells, would have no motivation to choose the TKT-L1 gene.

Additionally, Mack et al. teaches away from the use of transketolase-like 1 in the normal to cancerous cell comparison. Mack et al indicates that a comparison of normal to cancerous cells will reveal over or under expression of certain genes in cancerous as compared to normal cells, and that such genes are *important* in ascertaining whether tissue is normal or cancerous. (Para. 194 "By comparing . . . . ") By failing to include transketolase like-1 in Tables 21 or 22 which compare gene expression levels in normal to cancerous cells, when Mack et al. had knowledge of the gene as indicated in Table 17, Mack et al indicates that transketolase like-1 is not among those genes *important* in measuring expression levels to indicate whether or not a test sample is cancerous.

Furthermore, the ratio Mack et al. reports for TKT-L1 in Table 17 would further dissuade a skilled person from selecting TKT-L1 as an indicator molecule of abnormal cell proliferations. A more optimal indicator gene would be overexpressed in MetC versus Prim C (i.e. the opposite of what Table 17 reports) and would be overexpressed in PrimC versus NormC (not reported or suggested by Mack et al.) Hence, due to the underexpression in MetC compared to PrimC that Mack et al reports, a skilled person would be dissuaded from selecting TKT-L1 for a NormC to PrimC comparison.

Certain logical conclusions regarding the ratios of TKT-L1 in various cell types inconsistent with the claimed embodiments are also suggested by Mack et al. In the patent application of Mack et al, the expression level of cancer tissues has been compared with the expression level of normal healthy tissue and TKT-L1 has not been identified as overexpressed in cancer (see e.g. Tables 15 and 21). According to Mack et al paragraph 42, the ratio to determine overexpression between metastatic and normal tissue was 1.0 or greater, so TKT-L1's omission from the tables when TKT-L1 was known to Mack et al. suggests that TKT-L1 may be equal or underexpressed in metastasis versus normal tissue, contrary to the present claim 34.

> [0042] In Tables 1-26, the ratio provided represents liver metastasis samples from patients with known metastatic disease vs. tissue samples from normal colon tissue. In these samples, the identified genes are overexpressed in the metastatic samples, as the ratio is greater than one, preferably 1.5 or greater, more preferably 2.0 or greater. *Mack et al.* [Emphasis Added]

Hence, one of skill in the art might conclude from a reading of Mack et al. paragraph 42 and a review of the relevant Tables 15 and 21 presenting overexpression of MetC compared to NormC, that due to TKT-L1's omission from those tables but inclusion in Table 17, TKT-L1 must be *underexpressed* or equal in MetC compared to NormC, contrary to the teachings of the present claim 34 that TKT-L1 is *overexpressed* in cells of abnormal cell proliferations. In other words, whereas Mack et al. may suggest by the omission of TKT-L1 Table 21 that :

NormC TKT-L1 $\geq$ MetC TKT-L1,

The teaching of present claim 34 is, however:

NormC TKT-L1 < Abnormal Cell Proliferation TKT-L1

Hence, because Mack et al may suggest a conclusion contrary to the teaching of the present claims, Mack et al. teaches away from and would not yield the present claims obvious.

Alternatively, if the Table 21 legend in Mack et al page 180 is taken into account, a discrepancy between what Mack et al reports to be listed in paragraph 42, i.e., overexpression in a ratio of greater than 1.0, and what Mack et al reports to be listed in the Table, i.e., overexpression greater than 3.0, arises. Assuming the Table 21 only reports overexpression greater than 3.0 according to the legend rather than the description, the possibility that TKT-L1 could be overexpressed in MetC as compared to NormC by some ratio less than 3.0 but greater than 1.0, and hence not listed in Table 21, exists. However, such a finding would be extremely unusual, and Applicants must assume that Mack et al were thorough and would have reported such an unusual result in the relationship:

NormC TKT-L1 < MetC TKT-L1 < PrimC TKT-L1

Such relationship would be very unexpected and extraordinary, because persons skilled in the art would expect that a gene which is overexpressed in MetC compared to NormC, i.e. in cells which derive from PrimC, would be expressed in that (parent) primary cancer cells ("PrimC") in an equal or less amount, but not in a higher amount. Presuming the inventors of Mack et al were

thorough in their study, they would have noticed and reported in their description a gene which was identified to be underexpressed in MetC compared to PrimC (i.e. TKT-L1 in Table 17) and at the same time was identified to be overexpressed in MetC compared to NormC (yielding a ratio less than three and therefore not listed in table 21). Indeed, the hundreds of pages of tables of genes studied and reported by Mack et al. would indicate to a skilled person in the art that the inventors of Mack et al. were thorough in their reporting. Hence, Mack et al's omission of any mention of TKT-L1 in MetC versus NormC teaches away from the inference that TKT-L1 is overexpressed in MetC by some ratio between 1.0 and 3.0, or even more specifically, that TKT-L1 is overexpressed in PrimC.

Further, the Mack et al.'s discrepancy between the two thresholds, i.e. a ratio of greater than 1.0 in the description paragraph 42, and a ratio of greater than 3.0 in the Table 21 legend, indicates once more that Mack et al. does not provide motivation for a skilled person to take a one-time mentioned gene in a PrimC to MetC comparison as a putative candidate for use as indicator molecule for the detection of cancer cells. A person of skill in the art would face undue experimentation due to Mack. et al's discrepancies in reporting and omissions of TKT-L1 from the relevant tables.

Because the Examiner has not established a *prima facie* case of obviousness and because Mack et al. teaches away from the combination, the Applicant respectfully urges that an obviousness rejection based on Mack et al should not be issued.

III. CONCLUSION

Having fully responded to all matters raised in the Office Action, Applicants respectfully request withdrawal of the foregoing rejections and objection and submits that all claims are in condition for allowance. If there are any outstanding issues that might be resolved by an interview or an Examiner's amendment, the Examiner is requested to call Applicants' attorney at the telephone number shown below.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper,

including extension of time fees, to Deposit Account 50-0951 and please credit any excess fees to such deposit account.

Respectfully submitted,

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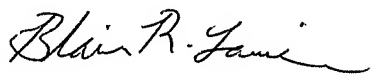

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